GW640385 (brecanavir)

Drug Class: **Protease Inhibitors**

Drug Description

GW640385 is an aspartyl protease inhibitor (PI) with structural similarities to amprenavir and potency against wild-type virus and multiple PI-resistant isolates. [1] [2]

HIV/AIDS-Related Uses

GW640385 is being investigated in Phase IIb trials for the treatment of HIV-1 infection resistant to currently available PIs.[3]

Pharmacology

GW640385 is an aspartyl PI more potent than first-generation PIs against wild-type HIV-1 and a wide range of PI-resistant viruses. Its low oral bioavailability is overcome by coadministration of low-dose ritonavir (RTV). A low-dose RTV booster administered with a single dose of GW640385 increases GW640385 plasma exposure approximately 30-fold.[4]

A two-week, randomized, double-blind, placebo-controlled trial was conducted in healthy participants to compare dosages of 800 mg GW640385 once-daily monotherapy; 100 mg or 250 mg GW640385 with RTV once daily; and 50, 150, or 300 mg GW640385 with RTV twice daily. All dosages were readily absorbed when administered with food, and all had similar times to maximum plasma concentration. Accumulation was less than dose proportional and ranged from two- to fivefold. Steady-state plasma concentrations were achieved by Day 15. Compared to 800 mg GW640385 monotherapy, median area under the concentration-time curve (AUC) levels were up to 85-fold, 52-fold, and 33-fold higher with 50mg, 150mg, and 300mg GW640385 twice-daily regimens, respectively. All twice daily dosages with RTV surpassed target plasma concentrations of 28 ng/ml, but once-daily regimens did not meet required concentrations for treating resistant virus.[5]

GW640385 retains activity against a panel of 55 viruses with an average of 8 mutations.[6] Laboratory studies in 30 clinical isolates showed minimal evidence for cross resistance between GW640385 and amprenavir, despite their chemical similarity. Amprenavir-associated I54L/M or I84V mutations alone did not appear associated with resistance to GW640385; however, GW640385 activity is reduced in the presence of the combination. GW640385 also appears to select for a mutation at A28S, a mutation not yet reported for any of the currently marketed PIs.[7] [8] [9]

Adverse Events/Toxicity

No serious adverse events have been observed with short-term administration of GW640385. No clinically significant cardiovascular events have been reported.

In one study, 34% of patients experienced at least one Grade 1 drug-related adverse event, including headache, dizziness and fatigue, and gastrointestinal symptoms. Two of ten patients taking 800 mg GW640385 monotherapy experienced a diffuse, erythematous macular rash within 10 days of therapy; both rashes resolved within two days of drug withdrawal. Fifty percent of patients on low-dose GW640385 with ritonavir booster experienced asymptomatic Grade 1 thyroid stimulating hormone (TSH) elevations, which returned to baseline over 2 to 3 weeks. No trends in T3 or T4 levels were observed.[10]

Drug and Food Interactions

GW640385 activity is additive in combination with other PIs and additive to synergistic with nucleoside reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors.[11]

Clinical Trials

For information on clinical trials that involve GW640385 (brecanavir), visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: GW640385 (brecanavir) AND HIV Infections.

GW640385 (brecanavir)

Dosing Information

Mode of Delivery: Oral.[12]

Dosage Form: Doses ranging from 50 mg to 800 mg once or twice daily have been studied in healthy people. Twice-daily doses of GW640385 combined with low-dose ritonavir booster have been chosen for study in HIV infected patients.[13]

Other Names

Brecanavir[14]

385[15]

640385[16]

GW0385[17]

VX-385[18]

Further Reading

ClinicalTrials.Gov - A Dose Ranging Study Of GW640385 Boosted With Ritonavir (RTV) In Comparison To A RTV-Boosted Protease Inhibitor (PI) In HIV-1 Infected PI-Experienced Adults. Available at:

GW640385 (brecanavir)

Further Reading (cont.)

Ford S, Reddy S, Anderson M, Murray S, Ng-Cashin J, and Johnson M. 640385, a novel HIV-1 protease inhibitor: Safety and pharmacokinetics following repeat administration with and without ritonavir in healthy subjects. Boston, Poster 563, 2005.

Spaltenstein A, Kazmierski WM, Miller JF, Samano V. Discovery of Next Generation Inhibitors of HIV Protease. Curr Top Med Chem. 2005;5(16):1589-607. PMID: 16375744

Manufacturer Information

GW640385 (brecanavir)
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Antivir Ther - 2004;9:S15

2. Antivir Ther - 2004;9:S16

3. ClinicalTrials.gov - A Dose Ranging Study Of GW640385 Boosted With Ritonavir (RTV) In Comparison To A RTV-Boosted Protease Inhibitor (PI) In HIV-1 Infected PI-Experienced Adults. Available at: http://www.clinicaltrials.gov/ct/show/NCT00242879. Accessed 01/25/06.

4. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

5. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

6. IAS Conf on HIV Pathogenesis and Treatment - 2nd, 2003. Abstract 541.

7. Antivir Ther - 2004;9:S15

8. Natl AIDS Treatment Advocacy Project (NATAP) - XIII International HIV Drug Resistance Workshop; June 8-12, 2004. Available at: http://www.natap.org/2004/HIVDRW/hivdrw_01.htm. Accessed 01/25/06.

9. Antivir Ther - 2004;9:S16

10. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

11. IAS Conf on HIV Pathogenesis and Treatment - 2nd, 2003. Abstract 541.

12. ClinicalTrials.gov - A Dose Ranging Study Of GW640385 Boosted With Ritonavir (RTV) In Comparison To A RTV-Boosted Protease Inhibitor (PI) In HIV-1 Infected PI-Experienced Adults. Available at: http://www.clinicaltrials.gov/ct/show/NCT00242879. Accessed 01/25/06.

13. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

14. Vertex Pharmaceuticals - Available at: http://www.vrtx.com/Pressreleases2005/pr121605.html. Accessed 01/25/06.

15. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

16. Conf Retroviruses Opportunistic Infect - 12th, 2005. Poster 563.

17. IAS Conf on HIV Pathogenesis and Treatment - 2nd, 2003. Abstract 541.

18. Natl AIDS Treatment Advocacy Project (NATAP) - XIII International HIV Drug Resistance Workshop; June 8-12, 2004. Available at: http://www.natap.org/2004/HIVDRW/hivdrw_01.htm. Accessed 01/25/06.